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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1628	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,637	SCHELLER ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-20* is/are pending in the application.

4a) Of the above claim(s) *15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-14,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/1/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments filed 3/01/2010 were entered.

Response to Arguments

2. Applicants' arguments, filed 3/01/2010, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

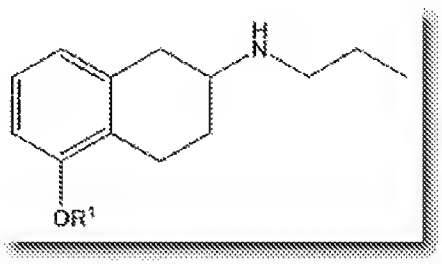
Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. **Claims 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over *van Vliet et al* (cited in a previous Action) in further view of *Wikstrom et al* (cited in a previous Action) and *Rodenhuis* (cited in a previous Action).**

6. As discussed in the previous Action, mailed on 9/02/2009, instant **claims 19-20** are drawn to a compound having the formula  in the (S)-configuration that, when administered to a human body, is cleaved, processed or metabolized to (S)-2-N-propylamino-5-hydroxytetralin.

7. *van Vliet et al* teach the racemic compound **2-N-propylamino-5-hydroxytetralin** (Table 1, Compound 11). More specifically, *van Vliet et al* disclose that the affinity of racemic 2-N-propylamino-5-hydroxytetralin for the dopamine receptor subtypes D_{2L}, D_3 and $D_{4.2}$ (based on antagonist competition binding studies using ^{3}H-spiperone) is 285, 0.75 and 76 (K_i nM) respectively (Table 2, Compound 11) seemingly indicating good selectivity for D_3 versus D_{2L} and $D_{4.2}$. However, as further noted by *van Vliet et al*, the D_2 receptor can exist in two states: a high-affinity state **and** a low-affinity state (Page 4234, Column 2) and the affinity of racemic 2-N-propylamino-5-hydroxytetralin for the **high**-affinity D_{2L} receptor (based on agonist competition binding studies using ^{3}H-N-0437) is 0.50 (K_i nM) (Table 2, Compound 11). Notably, based on these data, the difference between binding selectivity of high-affinity states of the D_{2L} and D_3 receptor is considerably decreased. Since agonist binding data using ^{3}H-N-0437 is "more relevant in assessing D_{2L}/D_3 receptor selectivity than the antagonist binding data

obtained with ^{3}H-spiperone" (Page 4234, Column 2), *van Vliet et al* teach that racemic 2-N-propylamino-5-hydroxytetralin is a potent D_{2L}/D_3 receptor agonist (albeit ***not*** a highly selective D_3 receptor agonist). In fact, 2-N-propylamino-5-hydroxytetralin appears to be among the most potent D_{2L}/D_3 receptor agonist tested by *van Vliet et al* (Page 4236, Table 2). For at least this reason, the skilled artisan would have found it *prima facie* obvious to formulate potent high-affinity D_{2L}/D_3 receptor agonist compositions specifically comprising 2-N-propylamino-5-hydroxytetralin in view of *van Vliet et al* with a reasonable expectation of success. However, *van Vliet et al* do not teach the (S) enantiomer of 2-N-propylamino-5-hydroxytetralin, nor do they teach a prodrug thereof.

8. *Wikstrom et al* teach enantiomeric separation of related aminotetralins to increase dopamine agonistic activity. Specifically, *Wikstrom et al* investigated the potency of enantiomers of the structurally and functionally related compound 5-hydroxy-2-(N,N-di-n-propylamino)tetralin (5-OH-DPAT) which "have been classified as less potent in the previous studies" (Page 217, Column 1, Paragraph 3). Significantly, *Wikstrom et al* report that the (S) enantiomer of the compound, having an ED_{50} of 3.7 nmol/kg, was significantly more potent than the racemic compound (Page 219, Table III, compound 1(S)) having an ED_{50} of 11 nmol/kg (Page 219, Column 2, Paragraph 6).

9. And *Rodenhuis* teaches that hydroxylated 2-aminotetralins "display limited activity upon oral administration. A major disadvantage of the hydroxylated 2-aminotetralins and other phenolic compounds is that they undergo considerable inactivation by glucuronidation in the gut and the liver. One of the strategies to circumvent the problem of the low oral bioavailability of

the hydroxylated 2-aminotetralins is to search for suitable prodrugs. Frequently investigated prodrugs of phenols are esters and carbamates" (Page 98, Chapter 6, Introduction, Paragraph 3).

10. Accordingly, one of ordinary skill in the art at the time the invention was made (desiring to formulate compositions comprising a potent D_{2L}/D_3 receptor agonist) would have been motivated to subject 2-N-propylamino-5-hydroxytetralin (which is a potent D_{2L}/D_3 receptor agonist as taught by *van Vliet et al*) to enantiomeric separation in view of *Wikstrom et al* (which teach enantiomeric separation of related aminotetralins to increase dopamine agonistic activity). Furthermore, one of ordinary skill in the art would have been motivated to formulate prodrugs of (S) 2-N-propylamino-5-hydroxytetralin as recited by instant claims 19-20 in view of *Rodenhuis* (who teaches ester and carbamate prodrugs of related compounds to overcome their low oral bioavailability). In doing so, said prodrug would necessarily be cleaved, processed or metabolized to 2-N-propylamino-5-hydroxytetralin upon administration to a human body, as recited by claim 19.

11. Accordingly, claims 19-20 are rejected as *prima facie* obvious.

12. Applicant traverses on a variety of grounds. First Applicant argues that "one of ordinary skill in the art looking for a compound that was selective for D_3 would not have any reason to select racemic 2-N-propylamino-5-hydroxytetralin from the 27 compounds tested in van Vliet" (Applicant Argument, Page 3). However, the reason or motivation to modify a reference to arrive at the claimed invention can be for a different purpose or to solve a different problem (in this case, to provide a compound selective for D_{2L} ***and*** D_3 as opposed to a compound selective for D_3). The fact that Applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the

differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58 (Bd. Pat. App. & Inter. 1985). Accordingly, although Applicant is correct that one of ordinary skill in the art - looking for a compound selective for D_3 - would **not** have selected 2-N-propylamino-5-hydroxytetralin from the 27 compounds tested in *van Vliet et al*, it is still the case that one of ordinary skill in the art - looking for a compound selective for D_{2L} ***and*** D_3 - **would** have selected 2-N-propylamino-5-hydroxytetralin from the 27 compounds tested in *van Vliet et al*. As such, Applicant's argument is not found persuasive.

13. Applicant next argues that "[t]he art a whole provides no motivation to select racemic 2-N-propylamino-5-hydroxytetralin" since, citing Table I of *Hacksell et al*, other aminotetralins are shown to be more active than 2-N-propylamino-5-hydroxytetralin (Applicant Argument, Page 4). Although *Hacksell et al* may disclose a preference for certain compounds, as stated by the court in *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004), "a prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed". Applicant additionally points to *Swart et al* (Toxicol Meth 3:279-290, 1993) which state that 2-N-propylamino-5-hydroxytetralin showed weak affinity in dopaminergic receptor binding studies (Page 289). However, this conclusion was based on the ability of 2-N-propylamino-5-hydroxytetralin to displace ^{3}H-N-0437 (Page 286). Accordingly, while *Swart et al* indicate that 2-N-propylamino-5-hydroxytetralin does not bind dopaminergic receptors as efficiently as N-0437, *Swart et al* do not overcome the data clearly demonstrating that 2-N-propylamino-5-hydroxytetralin possesses significant dopamine agonistic activity.

14. Applicant further argues that "the secondary cited documents, Wistrom and Rodenhuis, do not provide any motivation to select racemic 2-N-propylamino-5-hydroxytetralin, as neither of these documents disclose, teach, or suggest 2-N-propylamino-5-hydroxytetralin" (Applicant Argument, Page 4). Applicants are, however, reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091 (Fed. Cir. 1986). In the instant case, the secondary references are applied to demonstrate why one of ordinary skill in the art (having selected 2-N-propylamino-5-hydroxytetralin in view of *van Vliet et al*) would have been motivated to subject the compound to enantiomeric separation and formulate prodrugs thereof.

15. Applicant next argues that one of ordinary skill in the art would not have reasonably predicted that enantiomeric separation and prodrug formulation would provide the same and/or better results (Applicant Argument, Page 5). Applicants are reminded that obviousness does not require absolute predictability, only a reasonable expectation of success of obtaining similar properties. *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). In the instant circumstances, the skilled artisan would have reasonably predicted that enantiomeric separation of 2-N-propylamino-5-hydroxytetralin and prodrug formulation would provide a compound having the same and/or better results in view of *Wikstrom et al* and *Rodenhuis* as discussed above. Although Applicant is correct that *Wikstrom et al* do not teach enantiomeric separation of 2-N-propylamino-5-hydroxytetralin, they do teach enantiomeric separation of the structurally and functionally related compound 5-OH-DPAT and, based on their structural and functional relationship, one of ordinary skill in the art would have reasonably predicted enantiomeric

separation of 2-N-propylamino-5-hydroxytetralin would also provide compounds having the same and/or better activity. As stated by the court in *In re Deuel*, 51 F.3d 1552 (Fed Cir 1995) "[a] known compound may suggest its analogs or isomers, either geometic isomers (cis v. trans) or position isomers (e.g., ortho v. para)".

16. Applicant further argues that "it could not have been predicted that specifically the (S)-enantiomer would exhibit the pronounced and functional D_3 selectivity.... [or] that (S)-2-N-propylamino-5-hydroxytetralin would show purely agonistic activity" (Applicant Argument, Page 6). Yet, even assuming *arguendo* Applicant's assertion, as discussed above, the reason or motivation to modify a reference to arrive at the claimed invention can be for a different purpose or to solve a different problem (in this case, to provide a compound selective for D_{2L} ***and*** D_3 as opposed to a compound selective for D_3, for example). As stated in *In re Papesch*, 315 F.2d 381 (CCPA 1963), "[f]rom the standpoint of patent law, a compound and all its properties are inseparable". In the instant case, the D_3 selectivity of the *prima facie* obvious compound motivated by the prior art (for arguably different reasons) is merely a property or result of said compound. For this reason, whether someone of skill in the art would have predicted that the *prima facie* obvious compound would possess D_3 selectivity is not relevant for determining obviousness as asserted by Applicant in Applicant Arguments (Pages 6-7). **However**, a showing that the *prima facie* obvious compound possesses these unexpected properties could be considered evidence of **unexpected results** to overcome a rejection based on obviousness. Applicant makes this assertion at Page 7 of Applicant Arguments. As discussed above, one of ordinary skill in the art at the time the invention was made would have predicted (based on *van Vliet et al*) that the *prima facie* obvious compound (in view of *Wikstrom et al* and *Rodenhuis*)

would be a potent high-affinity D_{2L}/D_3 receptor agonist. As such, it is agreed that one of ordinary skill in the art would consider evidence that said compound is a ***selective D_3 agonist*** as unexpected. And, as correctly noted by Applicant, evidence of unexpected results can overcome a rejection based on obviousness. At the outset, Applicant is reminded that the claims must be drafted commensurate in scope with the unexpected results. In the instant case, the claims appear to be broader than the alleged unexpected results. However, and more importantly, the results presented by Applicant can not yet be considered unexpected. Specifically, Applicant argues that (S)-2-N-propylamino-5-hydroxytetralin binds with a Ki value of 7.6 nM to the D_3 receptor, with is 1000 times more selective compared to the D_1 or D_5 receptor, and 40 times more selective compared to the D_2 receptor (Applicant Argument, Page 7). Yet, as discussed in the previous Action, as taught by *van Vliet et al*, the D_2 receptor can exist in two states: a high-affinity state **and** a low-affinity state (Page 4234, Column 2). Whereas antagonist binding data obtained with ^{3}H-spiperone shows high D_3 selectivity, agonist binding data using ^{3}H-N-0437 shows little to no D_3 selectivity. Since agonist binding data using ^{3}H-N-0437 is "more relevant in assessing D_{2L}/D_3 receptor selectivity than the antagonist binding data obtained with ^{3}H-spiperone" (Page 4234, Column 2), *van Vliet et al* teach that racemic 2-N-propylamino-5-hydroxytetralin is a potent D_{2L}/D_3 receptor agonist (albeit ***not*** a highly selective D_3 receptor agonist). In the instant case, however, it is not clear whether Applicant's data (which indicate (S)-2-N-propylamino-5-hydroxytetralin binds with a Ki value of 7.6 nM to the D_3 receptor, with is 1000 times more selective compared to the D_1 or D_5 receptor, and 40 times more selective compared to the D_2 receptor (Applicant Argument, Page 7)) is based on data that takes into

account both affinity states of the D_2 receptor. Absent this information, it is impossible to determine whether the alleged D_3 selectivity accurately represents D_2/D_3 selectivity.

17. Accordingly, for all of the foregoing reasons, the rejection of claims is maintained.

18. **Claims 10-14 are is rejected under 35 U.S.C. 103(a) as being unpatentable over *van Vliet et al* in further view of *Wikstrom et al* and *Rodenhuis* as applied to claim 19 above, in further view of *den Daas et al* (cited in a previous Action).**

19. Instant claims 10-12 and 14 are drawn to compositions containing (S) 2-N-propylamino-5-hydroxytetralin or a prodrug thereof **and a pharmaceutically acceptable carrier or adjuvant**. More specifically, wherein the composition is adapted for transdermal, transmucosal or parenteral administration, as recited by instant claim 13.

20. As discussed above, *van Vliet et al* in further view of *Wikstrom et al* and *Rodenhuis* teach (S) 2-N-propylamino-5-hydroxytetralin and prodrugs thereof. However, none of the prior art teach the *prima facie* obvious composition further comprising a pharmaceutically acceptable carrier or adjuvant, or wherein the composition is adapted for transdermal, transmucosal or parenteral administration.

21. As discussed in the previous Action, *Rodenhuis* teaches that hydroxylated 2-aminotetralins "display limited activity upon oral administration" and suggest formulating prodrugs to overcome this problem (Page 98, Chapter 6, Introduction, Paragraph 3). In addition, *den Daas et al* teach "[a]nother possibility to avoid first-pass metabolism is the administration of compounds via the transdermal route" (Page 655, Column 2, Second Paragraph). Thus, noting that "[t]he next logical step in the transdermal application of dopamine agonists would be the use of transdermally applicated prodrugs" (Page 655, Column 2, Third Paragraph), *den Daas et al*

teach compositions comprising structurally and functionally related compounds and further comprising a pharmaceutically acceptable carrier or adjuvant, wherein the composition is adapted for transdermal, transmucosal or parenteral administration (Page 656, Column 1, First Paragraph). Accordingly, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to formulate the *prima facie* compositions taught by *van Vliet et al* in further view of *Wikstrom et al* and *Rodenhuis* with a pharmaceutically acceptable carrier or adjuvant, wherein the composition is adapted for transdermal delivery in view of *den Daas et al*. The skilled artisan would have been motivated to do so in order to avoid the risk of metabolic inactivation with a reasonable expectation of success.

22. Accordingly, instant claims 10-14 are rejected as *prima facie* obvious.

23. Since Applicant does not traverse the rejection of claims 10-14 beyond those arguments already discussed in detail above, the rejection of claims is maintained.

Conclusion

No new ground(s) of rejection are presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Padmanabhan "Paddy" Sreenivasan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1628

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642